7014537

MAIL STOP RCE
Attorney Docket No. 26569U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

GOLDMANN et al.		Conf. No.:	8794
Appl. No.:	10/521,455	Examiner:	SCHILLINGER, A.
Filed:	January 14, 2005	Art Unit:	3774
For:	**IMPLANT WITH ANTIBIOTIC LONG-TERM ACTION**		

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Dr. Helmut Goldmann declare as follows:

1. I am employed as a Director R & D Surgical Vascular Products, Aesculap AG in Tuttlingen, Germany and am engaged in R & D. I have been in my current position since 01.10.1997. My responsibilities include the development of vascular grafts.

2. I have reviewed the specification of United States Patent Application No. 10/521,455. I am an inventor of the subject matter claimed. I have reviewed the rejections to the pending claims set forth in the Official Action mailed from the United States Patent and Trademark Office on June 7, 2010. Additionally, I have reviewed the references cited by the Examiner as the subject of rejections regarding the patentability of the claimed subject matter.

3. Additionally, I have reviewed the presently pending claims, which are, in general, directed to an antibacterial vascular prosthesis prepared by specific process steps. Briefly, the vascular prosthesis is prepared by providing a porous basic structure, depositing silver onto the surface of the porous basic structure, and impregnating the silver coated porous basic structure with an absorbable material.

4. I have also studied the Official Action issued on June 7, 2010 in the present application. In particular, the claims have been rejected under 35 USC § 112, second paragraph as lacking sufficient antecedent basis. Further, the claims have been rejected under 35 USC § 103 as being unpatentable over Trogolo et al. (U.S. Patent No. 6,296,863), Sioshansi et al. (U.S. Patent No. 5,474,797), Ragheb et al. (U.S. Patent No. 4,873,904) and Shikani et al. (U.S. Patent No. 5,762,638) However, in contrast to the assertions in the Official Action, it is my belief and understanding that the claims are non-obvious and patentable over the cited references.

5. As evidence of this, I have **overseen the preparation of** and studied the experiments and data described herein below. The data described herein provides evidence that the antibacterial vascular prosthesis prepared by the specific process steps recited in the claims provides a better antibacterial effect than the prosthesis prepared by alternative methods.

6. ***MATERIALS AND METHODS***

A. ***Preparation of Prosthesis***

a. Double-velour knitted prostheses of polyester are clamped in a rotatable clamp device so that they hang freely as a bundle of parallel tubes with spaces between them. The clamp device is introduced into a vacuum chamber suitable for carrying out the IBAD technique, the vascular prostheses being vapor-deposited with silver and at the same time bombarded with argon ions. The coating operation is conducted until a silver layer thickness of 1300 Å is reached on the outside of the vascular prostheses or the fibers located there. If so desired, a primary coating can be affected by vapor-deposition of other metals. Silver is also forced into the pores or interstices between the fibers of the vascular prostheses, so that the fiber surfaces are coated at these locations too. However, the layer thickness is less there because of the "shadow effect" in the vapor-deposition. Determination of the amount of silver on the vascular prostheses (still without absorbable layer) has revealed that the proportion of silver relative to the total weight of the metallized prosthesis lies in the range of from 0.4 to 0.8% by weight.

b. The vascular prostheses coated in this way are removed from the clamp device and then impregnated in the usual manner with absorbable material at least on their outside, sealing off the porous structure. This impregnation can be done in the usual way with collagen, in which partial crosslinking with glutaraldehyde is affected. Preference is given to a likewise known coating with gelatin which is crosslinked with diisocyanate. As has been mentioned, bioactive substances can be introduced into the coating solution in order to develop the biological activity during the later absorption of the layer.

B. ***Comparison Test***

a. A vascular prosthesis prepared by the process described above (Section 6.A.a.), but **without** the absorbable impregnation layer (subsection b), was placed in phosphate buffer (pH 7.4) at 37.degree. C. The phosphate buffer was changed daily and the silver content in the previous phosphate buffer sample was determined. The test extended across a period of 365 days.

b. Under the same conditions, a vascular prosthesis prepared by the process described above **with** an absorbable impregnation layer of gelatin crosslinked with diisocyanate was examined (Section 6.A. a&b).

C. ***Artificial Infection***

a. A comparison was conducted using implants according to the presently claimed subject matter, and implants which, instead of having a silver layer on the basic structure, contained silver acetate incorporated in the absorbable coating. The comparison specimens were artificially infected with problem microbes and implanted in rabbits. They were explanted after 7 days. The comparison specimens were then incubated for 48 hours in CASO broth, after which a microbial count was conducted. The microbial colonization was determined microbiologically in 36 specimens.

7. **Results**

A. **Comparison Test**

a. **Vascular prosthesis *without* the absorbable impregnation layer:** The silver content in the removed phosphate buffer was initially 35 microgram/l and then fell rapidly, and then after 50 days slowly (15 microgram/l), and after 365 days it was ca. 5 microgram/l.

b. **Vascular prosthesis *with* the absorbable impregnation layer:** Although no silver was added to the gelatin, a high content of silver in the range of ca. 70 to 80 microgram/l was initially found in the phosphate buffer, and although it decreased slightly it remained high until the absorbable layer had largely broken up. It was not until after about 50 days that the silver content in the phosphate buffer had fallen to the level shown after 50 days by the vascular prosthesis not provided with the impregnation coating, after which time the release of the silver ions into the phosphate buffer was essentially the same as in the vascular prosthesis without impregnation coating.

c. This comparison shows that the silver layer was attacked via the impregnation coating, and silver ions were released into the impregnation coating, and these then entered the phosphate buffer at an increased rate and in increased number. The vascular prosthesis provided with the impregnation layer thereafter showed a comparable release of silver ions, which means that the initial strong release of silver has no negative effect on the long-term action.

B. **Artificial Infection**

a. It was found that, in the implants according to the presently claimed subject matter, only 22%, corresponding to 8 out of 36 implants, were colonized with a small number of microbes, whereas, in the implants with silver acetate in the absorbable coating, infection was found in 64%, corresponding to 23 out of 36 implants.

8. ***SUMMARY***

a. The above experimental data show that the vascular prosthesis of the presently claimed subject matter provides silver ions being release at an increased rate and in increased number.

b. Further, the results presented in the patent specification with respect to infection rates show that the infection rate is much lower for the vascular prosthesis prepared by the process of the presently claimed subject matter when compared to vascular prosthesis prepared with silver incorporated in the absorbable coating.

9. I herby further declare that the statement made herein of my own knowledge is true; and further that this statement was made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 81 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Hubert Goldmann — 2010-11-05

DECLARANT NAME — Date